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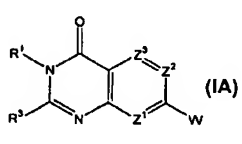
(54) Title: GUANIDINO-SUBSTITUTED QUINAZOLINONE COMPOUNDS AS MC4-R AGONISTS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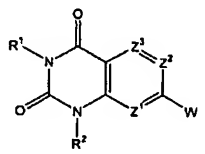
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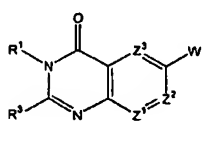
(IC)

(57) Abstract: A variety of small molecule, guanidine-containing molecules capable of acting as MC4-R agonists are provided. The compounds are useful in treating MC4-R mediated diseases when administered to subjects. The compounds have the structure IA, IB, and IC where the values of the variables are defined herein.

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AMENDED CLAIMS
[received by the International Bureau on 15 December 2004 (15.12.04);
original claims 1, 8, 10 amended; new claims 29-92 added; remaining claims unchanged (22 pages)]

$R^{4'}$ is selected from H, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, or heteroarylalkyl groups; and

pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, hydrates thereof, or solvates thereof.

2. The compound of claim 1, wherein one of $R^{1'}$ or $R^{2'}$ is a substituted or unsubstituted pyrrolidinylalkyl group.

3. The compound of claim 2, wherein one of $R^{1'}$ or $R^{2'}$ is a substituted or unsubstituted pyrrolidinylmethyl group or is a substituted or unsubstituted pyrrolidinylethyl group.

4. The compound of claim 1, wherein R^3 is H.

5. The compound of claim 1, wherein Z^1 is a CR^4 group, Z^2 is a CR^5 group, and Z^3 is a CR^6 group.

6. The compound of claim 1, wherein $R^{3'}$ is selected from substituted or unsubstituted cycloalkyl, polycyclic cycloalkyl, alkenyl, alkyl, or aryl groups.

7. The compound of claim 1, wherein R^1 is a 2,4-disubstituted phenylethyl group.

8. The compound of claim 1, wherein R^1 is selected from a phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-phenoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 2-fluoro-4-chlorophenylethyl, 2-fluoro-4-

heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, or alkylthioalkyl groups;

$R^{3'}$ is selected from H, or substituted or unsubstituted aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, or cycloalkylalkyl groups;

$R^{4'}$ is selected from H, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, or heteroarylalkyl groups; and

pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, hydrates thereof, or solvates thereof.

11. The compound of claim 10, wherein the heterocyclic ring formed by $R^{1'}$ and $R^{2'}$ and the nitrogen to which they are bound is a substituted piperazine.

12. The compound of claim 11, wherein the piperazine is substituted with a group selected from a phenylalkyl group, a substituted or unsubstituted phenyl group, an –alkyl-SCH_3 group, an indolylalkyl group, a morpholinylalkyl group, a pyridyl group, a piperidinyl group, or a tetrahydrofuranylalkyl group.

13. The compound of claim 10, wherein the heterocyclic ring formed by $R^{1'}$ and $R^{2'}$ and the nitrogen to which they are bound is a substituted piperidine.

14. The compound of claim 13, wherein the piperidine is substituted with a group selected from a phenylalkyl group, a substituted or unsubstituted phenyl group, an –alkyl-SCH_3 group, an indolylalkyl group, a morpholinylalkyl group, a pyridyl group, a piperidinyl group, or a tetrahydrofuranylalkyl group.

23. A method of treating an MC4-R mediated disease, comprising administering to a subject in need thereof, the compound according to any one of claims 10-19.

24. The method according to claim 23, wherein the disease is obesity or type II diabetes.

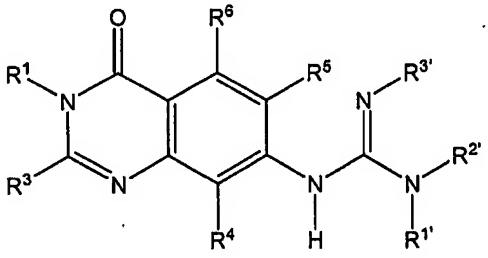
25. Use of a compound of any one of claims 1-8 in the preparation of a medicament for treating an MC4-R mediated disease.

26. The use of claim 25, wherein the MC4-R mediated disease is obesity or type II diabetes.

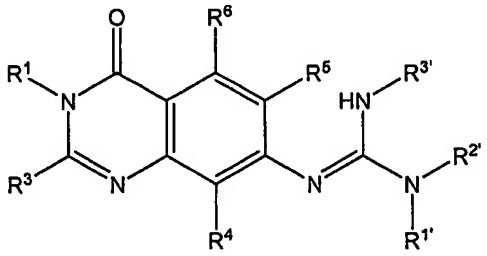
27. Use of a compound of any one of claims 10-19 in the preparation of a medicament for treating an MC4-R mediated disease.

28. The use of claim 27, wherein the MC4-R mediated disease is obesity or type II diabetes.

29. A compound of formula VA, VB, mixtures thereof, or pharmaceutically acceptable salts of the compound,



VA



VB

wherein

R^1 is selected from substituted or unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, or alkyl groups;

R^3 is selected from substituted or unsubstituted aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, or cycloalkylamino groups;

R^4, R^5, and R^6 are independently selected from H, Cl, I, F, Br, OH, NH_2, CN, NO_2, or substituted or unsubstituted alkoxy or alkyl groups;

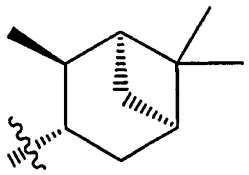
$R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl group; and

$R^{3'}$ is selected from substituted or unsubstituted cycloalkyl groups.

30. The compound of claim 29, wherein R^4, R^5, and R^6 are all H.

31. The compound of claim 29, wherein $R^{3'}$ is a substituted or unsubstituted polycyclic cycloalkyl group.

32. The compound of claim 31, wherein $R^{3'}$ is a substituted or unsubstituted polycyclic cycloalkyl group of formula VIII



VIII

33. The compound of claim 29, wherein R^1 is a substituted or unsubstituted arylalkyl group.

34. The compound of claim 33, wherein R^1 is a substituted phenylethyl group.

35. The compound of claim 34, wherein R^1 is a 4-substituted phenylethyl group or is a 2,4-disubstituted phenylethyl group.

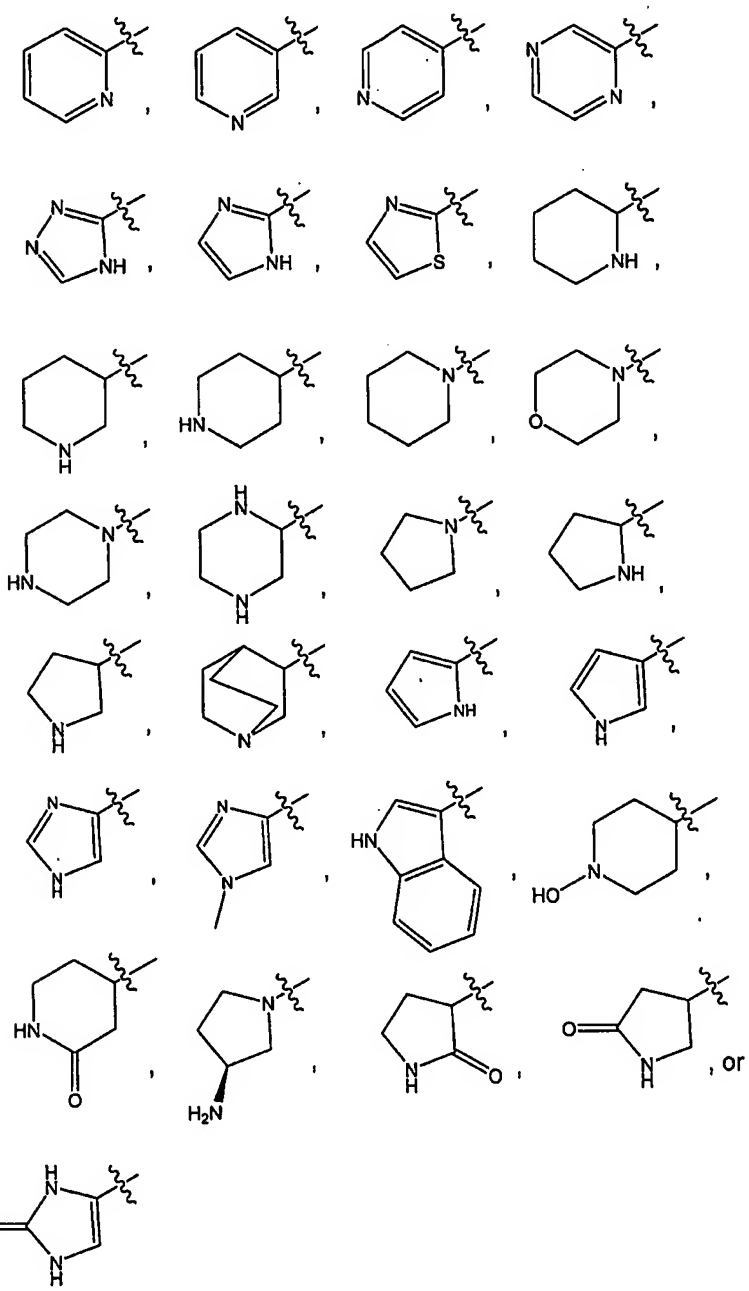
36. The compound of claim 34, wherein R^1 is selected from 2-fluoro-4-methoxyphenylethyl, 2-chloro-4-methoxyphenylethyl, 4-fluorophenylethyl, 4-chlorophenylethyl, 4-chloro-2-fluorophenylethyl, 2,4-dichlorophenylethyl, 4-bromophenylethyl, or 4-bromo-2-fluorophenylethyl groups.

37. The compound of claim 29, wherein R^1 is selected from phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-phenoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-fluorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 4-chloro-2-fluorophenylethyl, 4-bromo-2-fluorophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-fluorophenylethyl, 2,4-difluorophenylethyl, 2,4-dimethylphenylethyl, 2,4-dimethoxyphenylethyl, (2-pyridyl)ethyl, (3-pyridyl)ethyl, (4-pyridyl)ethyl, (pyridyl)(hydroxymethyl)ethyl, or (phenyl)(hydroxymethyl)ethyl groups.

38. The compound of claim 29, wherein R^3 is selected from substituted or unsubstituted heterocyclyl groups, or substituted or unsubstituted heteroaryl groups.

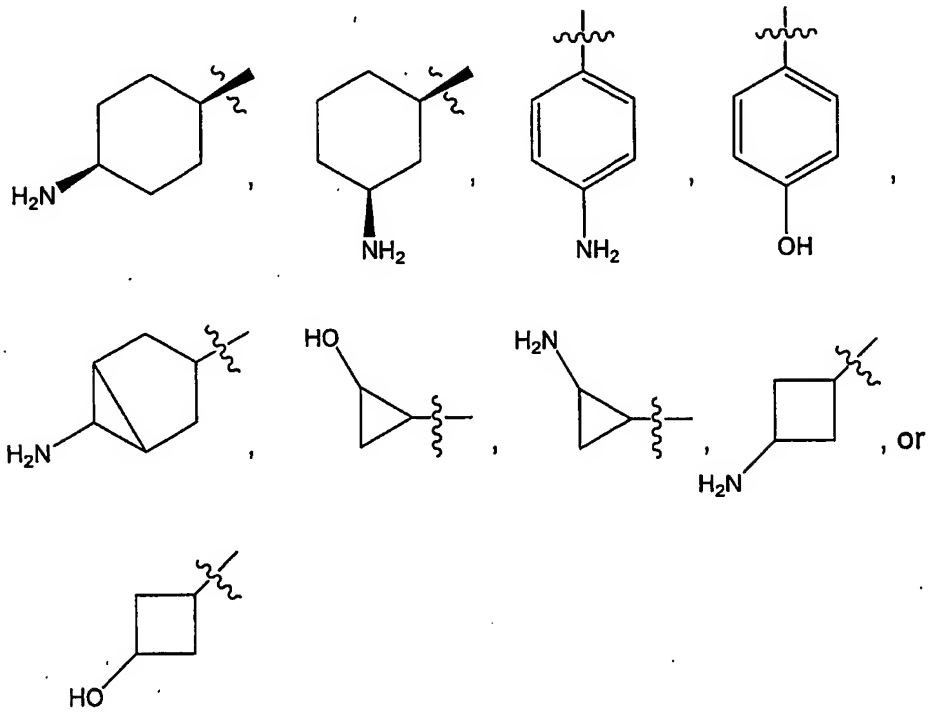
39. The compound of claim 38, wherein R^3 is selected from substituted or unsubstituted pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, furanyl, pyrrolidinyl, pyrrolyl, thiophenyl, tetrahydrothiophenyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrazinyl, thiazolyl, pyrimidinyl, quinuclidinyl, indolyl, imidazolyl, triazolyl, tetrazolyl, or pyridazinyl groups.

40. The compound of claim 29, wherein R^3 is selected from heteroaryl or heterocyclyl groups of formula



which may be additionally substituted or may be unsubstituted.

41. The compound of claim 29, wherein R^3 is selected from aryl or cycloalkyl groups of formula



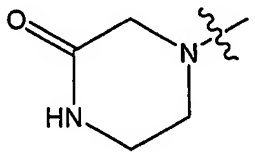
which may be additionally substituted or may be unsubstituted.

42. The compound of claim 29, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted piperazinyl group.

43. The compound of claim 42, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazinyl group that is substituted with at least one group selected from, fluoromethyl, difluoromethyl, or trifluoromethyl groups.

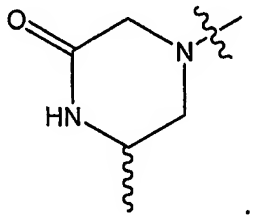
44. The compound of claim 42, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazinyl group comprising at least one carbonyl group such that the piperazinyl group is a piperazinone that may be additionally substituted.

45. The compound of claim 44, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound form a piperazinone of formula

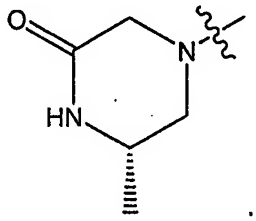


which may be additionally substituted.

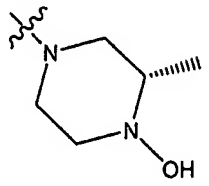
46. The compound of claim 45, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound form a piperazinone of formula



47. The compound of claim 46, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound form a piperazinone of formula



48. The compound of claim 42, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazinyl group of formula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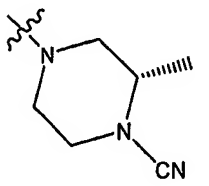
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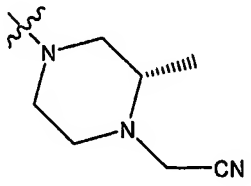
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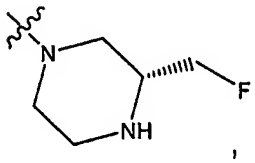
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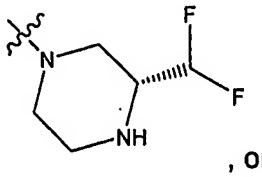
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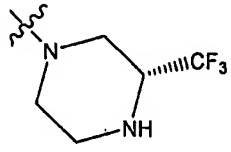
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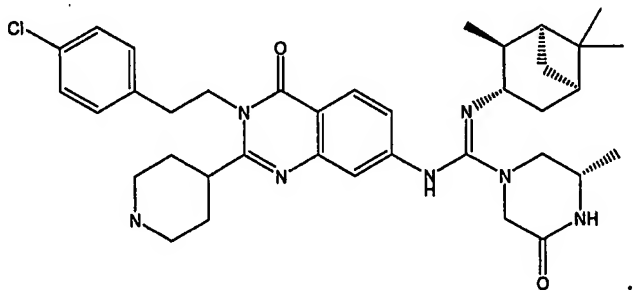
49. The compound of claim 29, wherein the compound is a compound of formula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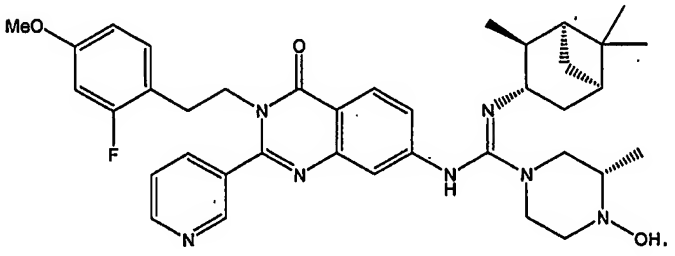
50. The compound of claim 29, wherein the compound is a compound of formula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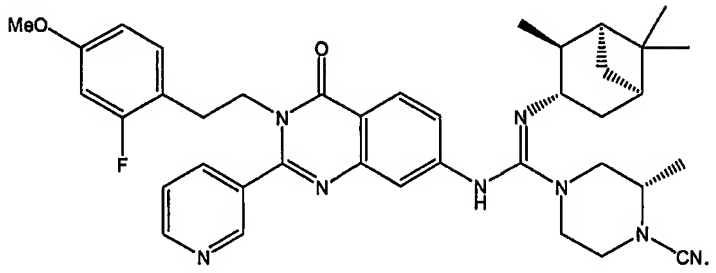
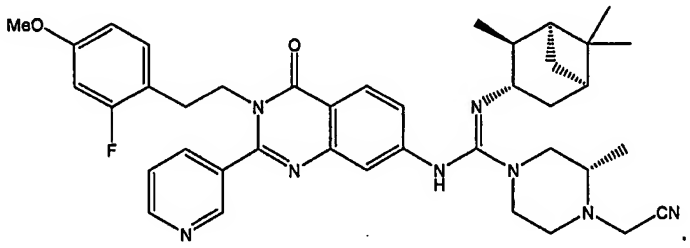
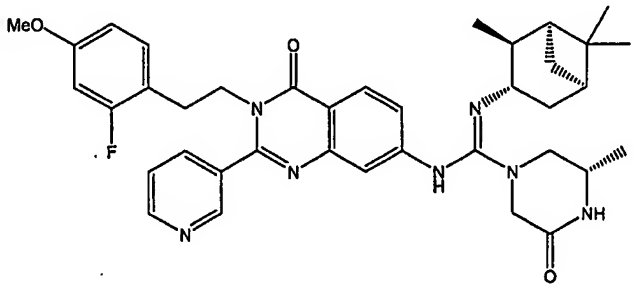
51. The compound of claim 29, wherein the compound is a compound of formula



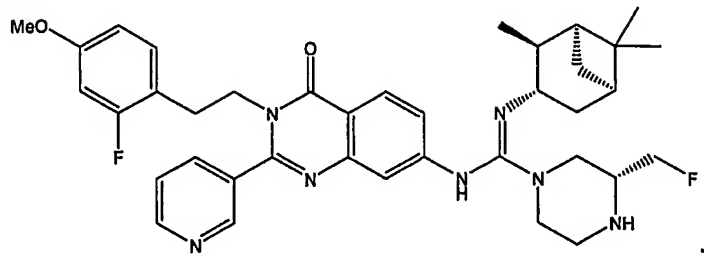
52. The compound of claim 29, wherein the compound is a compound of formula



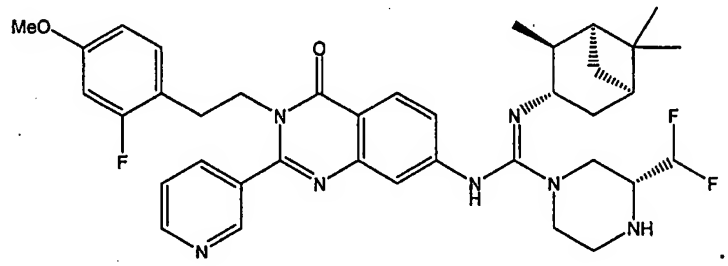
53. The compound of claim 29, wherein the compound is a compound of formula



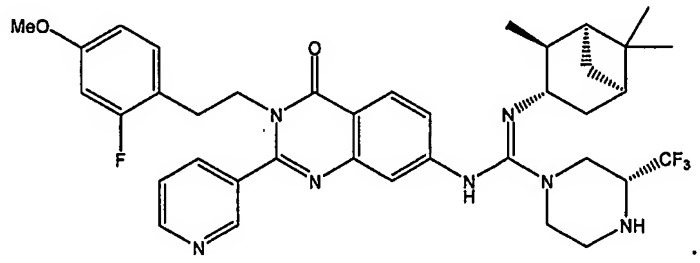
54. The compound of claim 29, wherein the compound is a compound of formula



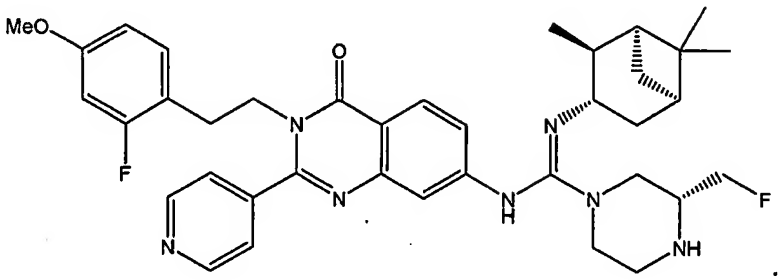
55. The compound of claim 29, wherein the compound is a compound of formula



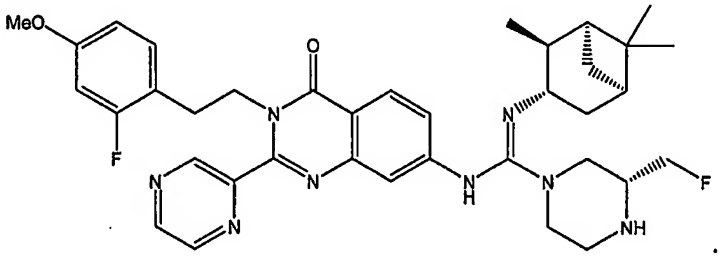
56. The compound of claim 29, wherein the compound is a compound of formula



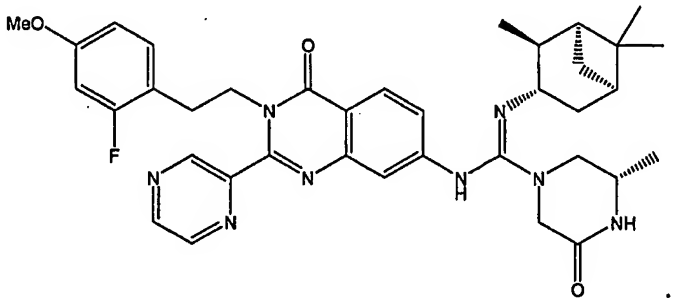
57. The compound of claim 29, wherein the compound is a compound of formula



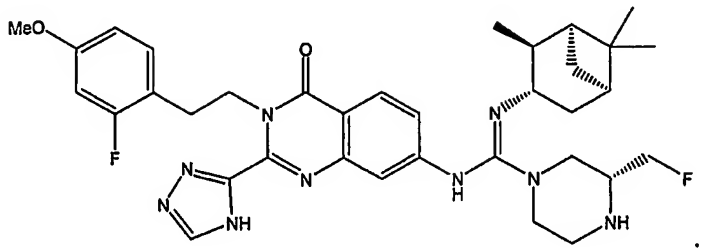
58. The compound of claim 29, wherein the compound is a compound of formula



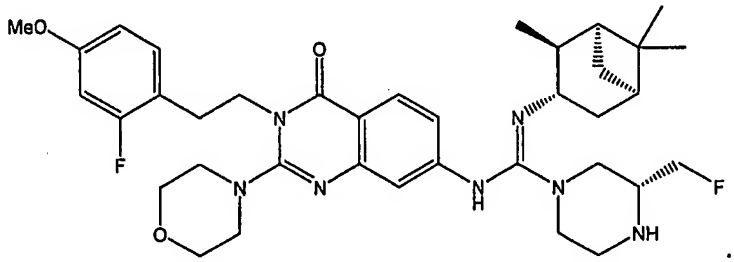
59. The compound of claim 29, wherein the compound is a compound of formula



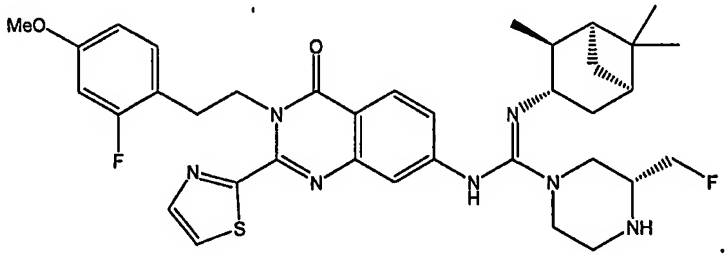
60. The compound of claim 29, wherein the compound is a compound of formula



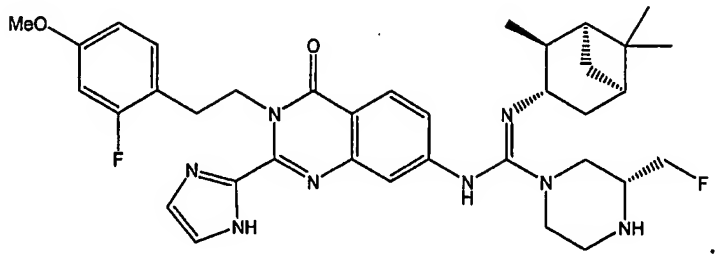
61. The compound of claim 29, wherein the compound is a compound of formula



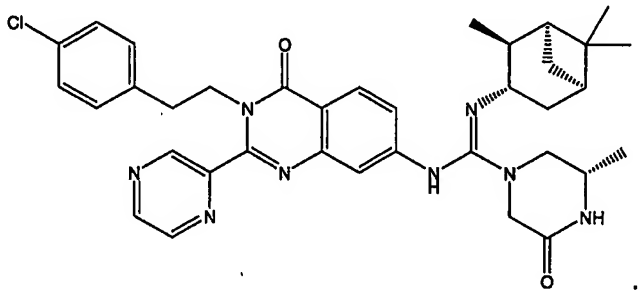
62. The compound of claim 29, wherein the compound is a compound of formula



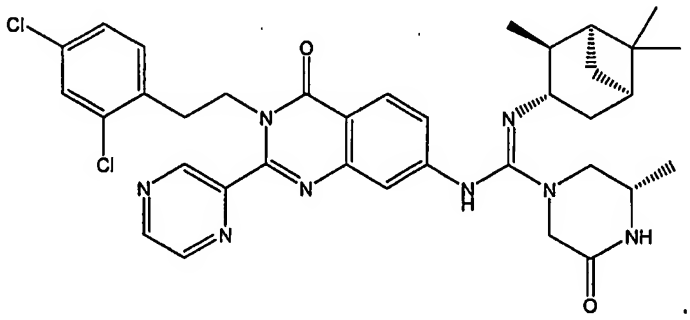
63. The compound of claim 29, wherein the compound is a compound of formula



64. The compound of claim 29, wherein the compound is a compound of formula



65. The compound of claim 29, wherein the compound is a compound of formula



66. A pharmaceutical formulation comprising the compound of any one of claims 29-65 and a pharmaceutically acceptable carrier.

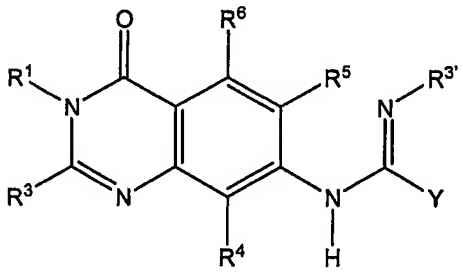
67. A method of treating an MC4-R mediated disease, comprising administering to a subject in need thereof, the compound of any one of claims 29-65.

68. The method according to claim 67, wherein the disease is obesity or type II diabetes.

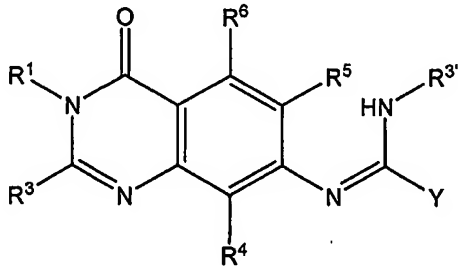
69. The method according to claim 67, wherein the compound exhibits a $t_{1/2}$ value of less than 35 hours in a tissue with high blood perfusion.

70. The method according to claim 69, wherein the tissue with high blood perfusion is selected from a brain, a liver, a kidney or a heart.

71. A compound of formula VIIA, VIIB, mixtures thereof, or pharmaceutically acceptable salts of the compound,



VIIA



VIIB

wherein

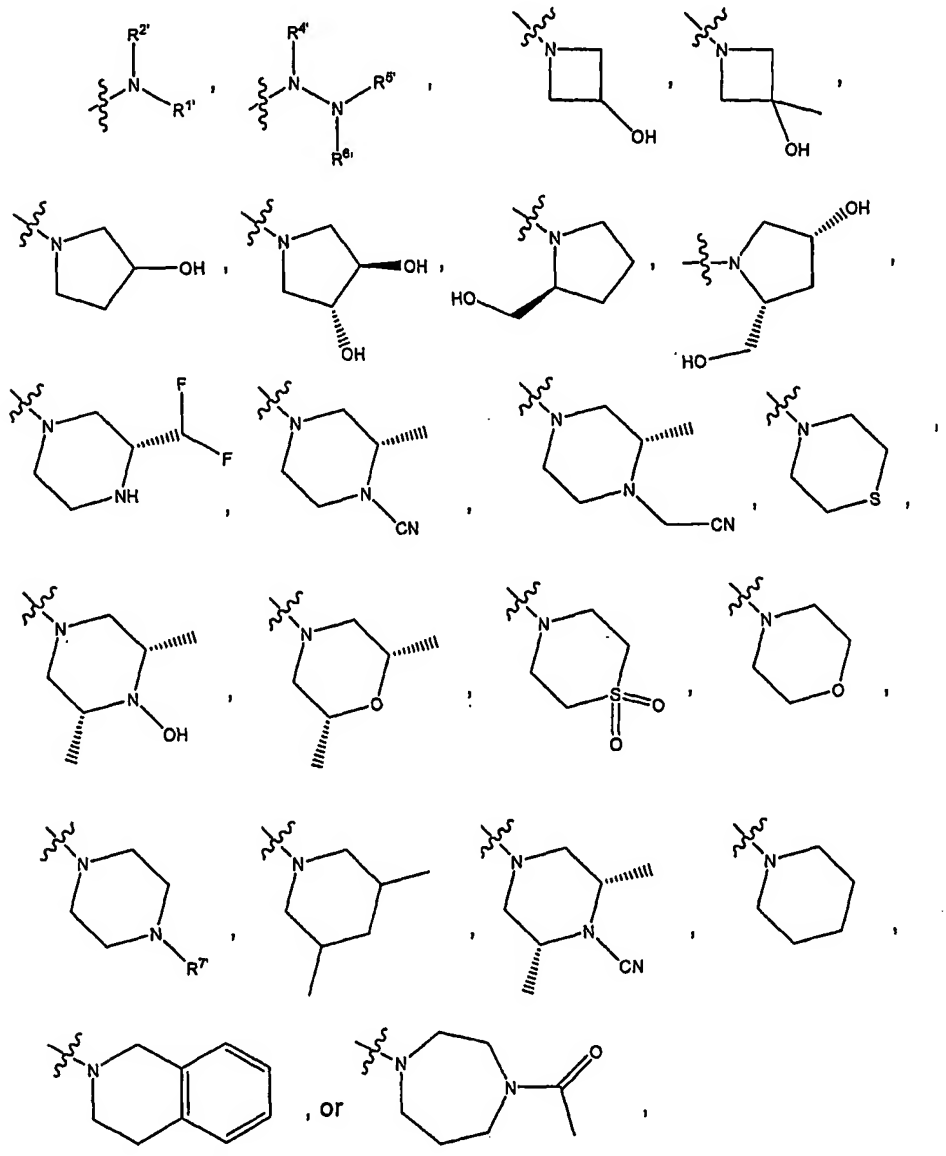
R^1 is selected from substituted or unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, or alkyl groups;

R^3 is selected from H or substituted or unsubstituted arylalkyl, heteroarylalkyl, alkoxy, alkylamino, dialkylamino, aryl, heteroaryl, heterocyclyl, cycloalkyl, aminocycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, or alkyl groups;

R^4, R^5, and R^6 are independently selected from H, Cl, I, F, Br, OH, NH_2, CN, NO_2, or substituted or unsubstituted alkoxy or alkyl groups;

$R^{3'}$ is selected from H or substituted or unsubstituted aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, or cycloalkylalkyl groups; and

Y is selected from a moiety of formula



wherein

$R^{1'}$ is selected from substituted or unsubstituted alkyl groups;

$R^{2'}$, $R^{4'}$, and $R^{5'}$ are independently selected from H or substituted or unsubstituted alkyl groups;

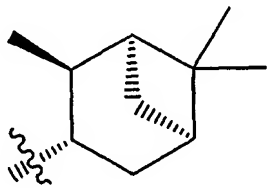
$R^{6'}$ is selected from substituted or unsubstituted alkyl groups; or $R^{5'}$ and $R^{6'}$, together with the nitrogen to which they are bound, form a heterocyclyl or heteroaryl group; and

$R^{7'}$ is selected from CN, or substituted or unsubstituted alkyl, aryl, or arylalkyl groups.

72. The compound of claim 71, wherein R^4, R^5, and R^6 are all H.

73. The compound of claim 71, wherein $R^{3'}$ is a substituted or unsubstituted polycyclic cycloalkyl group.

74. The compound of claim 73, wherein $R^{3'}$ is a substituted or unsubstituted polycyclic cycloalkyl group of formula VIII



VIII

75. The compound of claim 71, wherein R^1 is a substituted or unsubstituted arylalkyl group.

76. The compound of claim 75, wherein R^1 is a substituted phenylethyl group.

77. The compound of claim 76, wherein R^1 is a 4-substituted phenylethyl group or is a 2,4-disubstituted phenylethyl group.

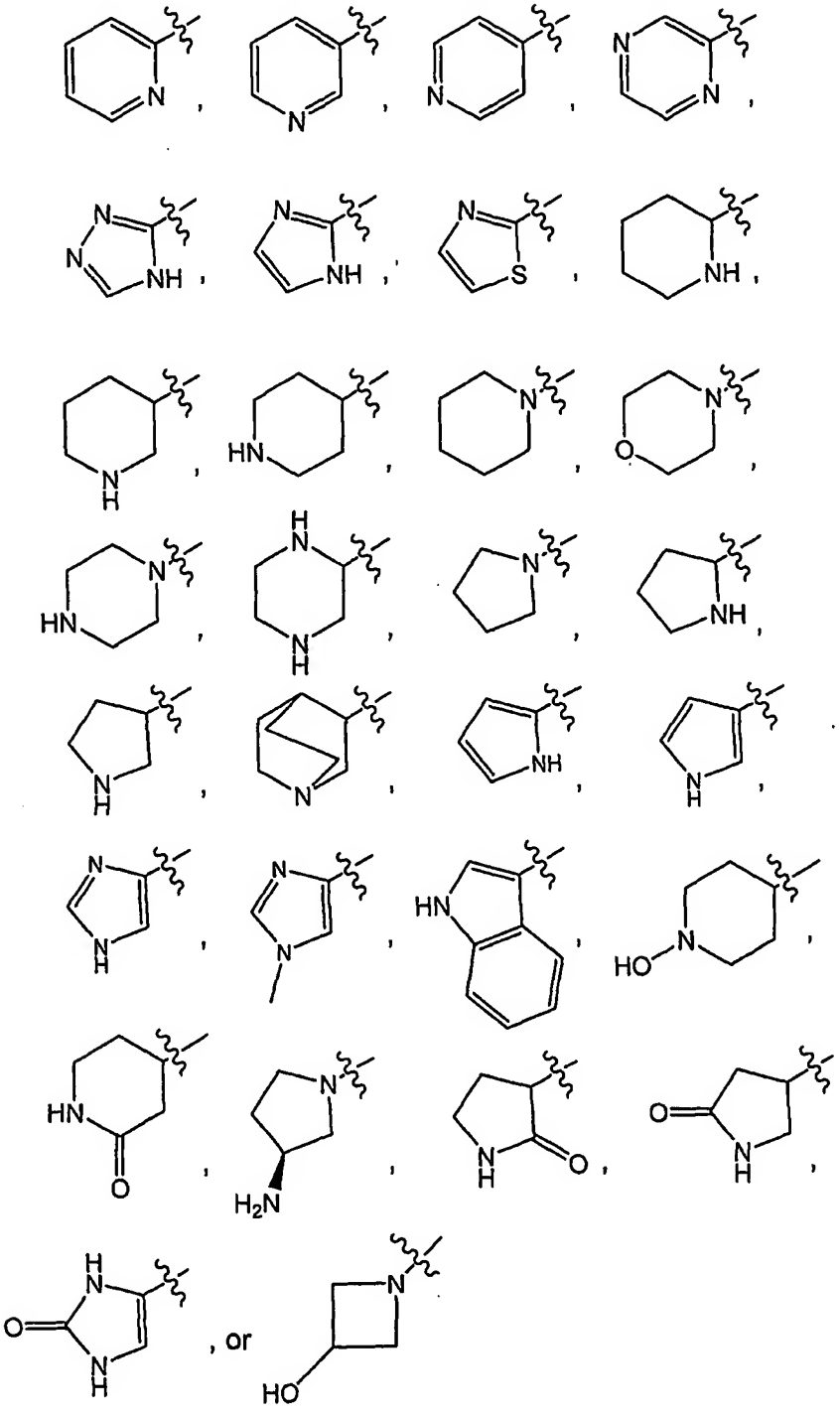
78. The compound of claim 75, wherein R^1 is selected from 2-fluoro-4-methoxyphenylethyl, 2-chloro-4-methoxyphenylethyl, 4-fluorophenylethyl, 4-chlorophenylethyl, 4-chloro-2-fluorophenylethyl, 2,4-dichlorophenylethyl, 4-bromophenylethyl, or 4-bromo-2-fluorophenylethyl groups.

79. The compound of claim 78, wherein R^3 is selected from substituted or unsubstituted heterocyclyl groups or substituted or unsubstituted heteroaryl groups.

80. The compound of claim 79, wherein R^3 is selected from substituted or unsubstituted pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, furanyl, pyrrolidinyl, pyrrolyl, thiophenyl, tetrahydrothiophenyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrazinyl, thiazolyl, pyrimidinyl, quinuclidinyl, indolyl, imidazolyl, triazolyl, tetrazolyl, or pyridazinyl groups.

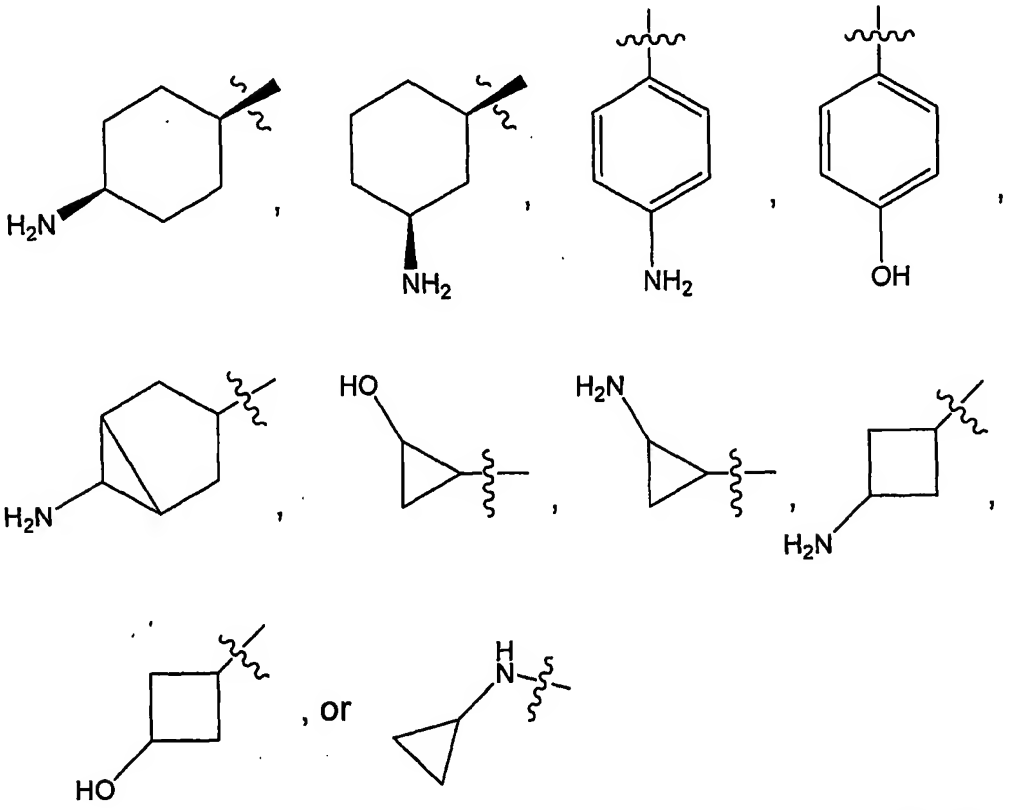
81. The compound of claim 71, wherein R^1 is selected from phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-phenoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-fluorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 4-chloro-2-fluorophenylethyl, 4-bromo-2-fluorophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-fluorophenylethyl, 2,4-difluorophenylethyl, 2,4-dimethylphenylethyl, 2,4-dimethoxyphenylethyl, (2-pyridyl)ethyl, (3-pyridyl)ethyl, (4-pyridyl)ethyl, (pyridyl)(hyd-roxymethyl)ethyl, or (phenyl)(hydroxymethyl)ethyl groups.

82. The compound of claim 71, wherein R^3 is selected from heteroaryl or heterocyclyl groups of formula



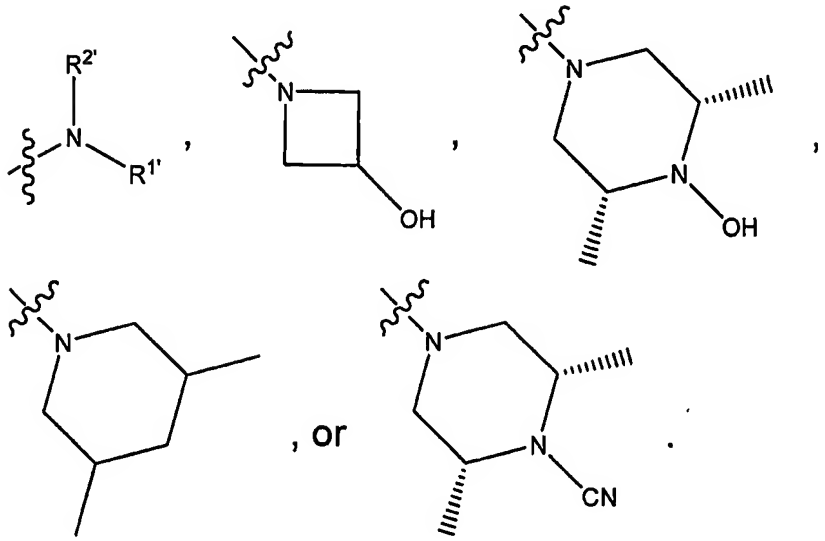
which may be additionally substituted or may be unsubstituted.

83. The compound of claim 71, wherein R^3 is selected from aryl, cycloalkyl, or aminocycloalkyl groups of formula

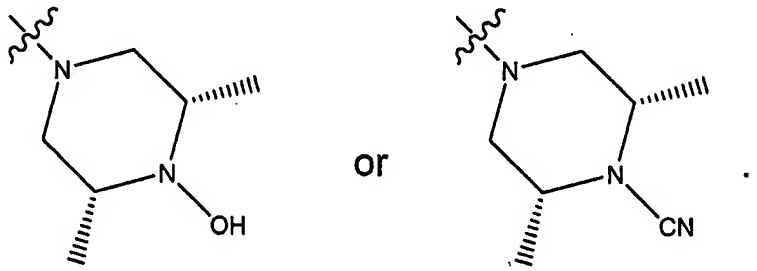


which may be additionally substituted or may be unsubstituted.

84. The compound of claim 71, wherein **Y** is selected from



85. The compound of claim 84, wherein **Y** is selected from



86. A pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of any one of claims 71-85.

87. A method of treating an MC4-R mediated disease, comprising administering to a subject in need thereof, the compound of any one of claims 71-85.

88. The method according to claim 87, wherein the disease is obesity or type II diabetes.

89. The method according to claim 88, wherein the compound exhibits a $t_{1/2}$ value of less than 35 hours in a tissue with high blood perfusion.

90. The method according to claim 89, wherein the tissue with high blood perfusion is selected from a brain, a liver, a kidney or a heart.

91. Use of a compound of any one of claims 29-66 or 71-85 in the preparation of a medicament for treating an MC4-R mediated disease.

92. The use of claim 91, wherein the MC4-R mediated disease is obesity or type II diabetes.